TESIS DE DOCTORADO

ACTINIC CHEILITIS PREVALENCE AND RISK FACTORS: A CROSS-SECTIONAL, MULTI-CENTRE STUDY IN A POPULATION AGED 45 YEARS AND OVER IN GALICIA-SPAIN

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Actinic cheilitis prevalence and risk factors: A cross-sectional, multi-centre study in a population aged 45 years and over in Galicia-Spain

Dña. María Isabel Rodríguez Blanco

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Actinic cheilitis prevalence and risk factors: A cross-sectional, multi-centre study in a population aged 45 years and over in Galicia-Spain

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Actinic cheilitis prevalence and risk factors: A cross-sectional, multi-centre study in a population aged 45 years and over in Galicia-Spain

En Santiago de Compostela, 14 de noviembre de 2020

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RESUMEN

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1. RESUMEN

INTRODUCCIÓN

La queilitis actínica (QA) es una patología que afecta principalmente al bermellón del labio inferior dando lugar a alteraciones clínicas y patológicas. La QA se considera mayoritariamente una forma superficial de carcinoma espinocelular (CE) y el principal factor de riesgo en su desarrollo es la exposición solar crónica (1).

QA es la denominación más comúnmente utilizada para describir esta entidad (2,3). El término "QA" ha sido considerado inapropiado por algunos autores por dos motivos. En primer lugar, la palabra "queilitis" implica un proceso inflamatorio que no es el hecho predominante en la QA. Además, la palabra "actínica" deriva del griego *aktin* que significa rayo, pero la QA se ha asociado tan solo con la radiación solar y no con otro tipo de radiación. En segundo lugar, la QA ha sido probablemente utilizada por algunos dermatólogos para referirse a otros cambios originados por la radiación ultravioleta sobre el labio como, por ejemplo, la elastosis solar, la atrofia solar o las telangiectasias. A pesar de su imperfección, QA es el término más frecuentemente utilizado en la literatura científica y por eso se ha elegido para esta tesis doctoral, ya que el uso de nomenclatura uniforme es necesario para mantener

una comunicación óptima entre clínicos, cirujanos y patólogos en todo el mundo (2).

En el año 2005, la Organización Mundial de la Salud (OMS) acuñó el término *potentially oral malignant disorders* para englobar lesiones orales con predisposición a una posible transformación maligna (4-6) y la QA estaba incluida entre ellas.

La QA es considerada por muchos autores un CE superficial del labio, del mismo modo que sucede con las queratosis actínicas en la piel (1,3,7-10). Aunque ha habido mucha especulación a este respecto, la tasa de progresión de QA a CE invasivo se desconoce, debido a la ausencia de estudios prospectivos bien diseñados, con seguimiento a largo plazo y con confirmación histológica sistemática. La semi-mucosa labial es además un área de alto riesgo de localización de los CE invasivos por su potencial metastático (8,11,12) y, por lo tanto, es fundamental profundizar en la epidemiología de la QA, considerada una forma superficial de CE que puede eventualmente progresar a un CE invasivo.

El número de publicaciones referentes a la epidemiología de la QA es realmente escaso (13-27). Los datos relacionados con la prevalencia de la QA están basados en estudios metodológicamente heterogéneos, la mayoría de ellos llevados a cabo en poblaciones específicas de Sudamérica y ninguno de ellos es un estudio multicéntrico. La comparación de los resultados de los mismos es difícil debido a varias razones, entre ellas la ausencia de una definición única de QA, la posible inclusión de otras patologías inflamatorias o neoplásicas distintas a la QA, las diferentes edades y

sexos de los sujetos incluidos o el análisis no homogéneo de posibles factores de riesgo como el fototipo de Fitzpatrick, la exposición solar previa o el consumo de alcohol o tabaco. La ingesta enólica y el hábito tabáquico se han relacionado con el cáncer de la cavidad oral (28-30) y también con el cáncer de labio, especialmente en aquellos pacientes acostumbrados a dejar el cigarrillo sobre el labio (31). La influencia del tabaco en el desarrollo de QA es controvertida, pero hasta la fecha no se ha establecido una relación causa-efecto (3), aunque parece evidente que la exposición constante al calor generado por la combustión de los cigarrillos puede agravar el aspecto de la enfermedad en sujetos expuestos crónicamente a la radiación solar (3,14,21,32). Por todo lo expuesto, la prevalencia publicada de QA en los distintos estudios tiene un rango amplio que abarca desde un 0,9% (15) hasta un 43,24% (16).

Tal como se mencionó previamente, a pesar de que la radiación solar es el principal factor de riesgo de la QA, existe poca evidencia acerca del uso de fotoprotección específica dirigida a la región labial. La aplicación de fotoprotección labial de forma adecuada es la primera y principal medida para prevenir el desarrollo de QA (23,33-37); a pesar de esto, se ha prestado poca atención a los hábitos de fotoprotección dirigidos específicamente a los labios (33,38,39) y existen muy pocos estudios que hayan investigado esta cuestión (40-43).

Las manifestaciones clínicas asociadas a la QA son la presencia de sequedad labial, tacto rugoso y descamación, y en ocasiones pueden aparecer pliegues marcados, fisuras o erosiones (8,44). De

Oliveira Ribeiro *et al*. propusieron los siguientes signos clínicos para establecer el diagnóstico de QA (24):

1. Descamación: presencia de escamas
2. Fisuras verticales: líneas que se extienden a la dermis subyacente
3. Atrofia: depresión del labio como resultado del adelgazamiento de la dermis o epidermis
4. Eritema: enrojecimiento del labio causado por vasodilatación
5. Manchas: cambio de color de la mucosa normal sin elevación o depresión alguna
6. Aspecto moteado: presencia simultánea de parches eritematosos y blanquecinos
7. Placa: lesión sólida, elevada de superficie plana > 1 cm de diámetro
8. Ulceración: disrupción del epitelio con exposición del tejido conectivo subyacente
9. Demarcación borrosa entre el borde de la semi-mucosa labial y la piel de la cara

La palpación es un componente importante de la exploración clínica y la QA se ha asociado con un tacto similar a un papel de lija fino (2). La presencia de infiltración, erosión mantenida en el tiempo,

ulceración, sangrado, atrofia y la ausencia de un límite preciso de la semi-mucosa pueden ser indicadores de progresión a CE (1,9,32,36,37).

La QA normalmente se describe como un cuadro asintomático, pero algunos estudios han descrito síntomas asociados; el 16,47% de pacientes con QA experimentaron dolor en un estudio (20) y el 34,48% (44) y 24,7% (37) de pacientes con QA en otros dos estudios refirieron ardor y picor, respectivamente.

La evidencia confirma que el aspecto clínico de la QA tiene una escasa correlación con el grado de displasia celular; aunque la precisión diagnóstica puede incrementarse con las nuevas técnicas de imagen (como la dermatoscopia o la microscopía confocal), sigue siendo necesario un seguimiento cercano de estos pacientes y se debe realizar una biopsia de las lesiones sospechosas para poder descartar un CE invasivo, que es el diagnóstico diferencial más importante de la QA (2,8,32,36,37,44,45).

Galicia es una comunidad autónoma localizada en el noroeste de España. Su población total en el año 2016 fue 2.718.525 habitantes (Instituto Gallego de Estadística, http:www.ige.eu), constituyendo la 5ª región más poblada de España.

Un problema realmente importante al que se enfrenta la comunidad autónoma gallega es el progresivo incremento etario de la población. Sujetos con una edad superior a los 65 años constituyeron el 24,31% de la población total en el año 2016, el 24,56% en el año 2017 y el 24,89% en el año 2018. El crecimiento vegetativo de la población gallega en esos años fue -12.695, -13.517 y -15.833,

respectivamente (Instituto Gallego de Estadística, http:www.ige.eu). El envejecimiento de la población es un motivo de preocupación en todos los países industrializados y, dentro de Europa, Galicia es una de las regiones con la mayor tasa proyectada de dependencia por edad avanzada en el año 2050 (46).

JUSTIFICACIÓN DEL ESTUDIO

La epidemiología de la QA ha sido escasamente analizada en el pasado. La mayor parte de los estudios publicados se han realizado en poblaciones específicas de Sudamérica, mayoritariamente en Brasil, pero no se dispone de estudios epidemiológicos multicéntricos y con un diseño prospectivo.

La exposición solar es el factor de riesgo más importante para el desarrollo de QA. Sin embargo, existen muy pocos estudios que hayan analizado los beneficios de una fotoprotección labial específica, en comparación con las numerosas publicaciones relativas a la fotoprotección de la piel. La escasa evidencia disponible muestra que la población general no suele utilizar rutinariamente un fotoprotector dirigido a la región labial.

Las manifestaciones clínicas de la QA han sido descritas en varios estudios, pero ninguno de ellos ha hecho referencia a los factores de riesgo específicos relacionados con cada una de las formas clínicas de QA. Además, marcadores de daño actínico crónico como las queratosis actínicas o los lentigos solares y sus posibles correlaciones no han sido analizadas en los pacientes con QA.

Con el fin de dar respuesta a todo lo expuesto, se diseñó un estudio multicéntrico transversal en un país con predominio de población caucásica, para evaluar la prevalencia de QA, analizar sus factores de riesgo y manifestaciones clínicas e investigar el uso de fotoprotección específica en los labios.

OBJETIVOS

El objetivo principal fue determinar la prevalencia de QA en la comunidad autónoma de Galicia, España en la población con edad igual o superior a 45 años.

Los objetivos secundarios fueron: (1) describir los factores de riesgo de QA en la población del estudio, (2) establecer el perfil clínico y epidemiológico de los pacientes con QA, (3) investigar los hábitos de los pacientes relacionados con la fotoprotección labial y su asociación con la exposición solar, (4) describir las diferentes manifestaciones clínicas de la QA y sus posibles factores de riesgo y (5) evaluar los marcadores de daño actínico y sus factores de riesgo en los pacientes con QA.

MATERIAL Y MÉTODOS

Se diseñó un estudio descriptivo, transversal, multicéntrico en la comunidad autónoma de Galicia, localizada en el noroeste de España. Ocho hospitales participaron en el estudio y los datos de los pacientes fueron recopilados prospectivamente desde el 12 de Enero del año 2016 hasta el 31 de Enero del año 2017.

Los pacientes ≥ 45 años catalogados como “Primera Visita” que acudieron a la consulta general de Dermatología de cada uno de los dermatólogos investigadores fueron consecutivamente reclutados una vez a la semana durante el período del estudio. Aquellos pacientes que no pudieron entender o contestar las cuestiones relativas a su historia clínica fueron excluidos.

Los datos del estudio fueron recopilados por los dermatólogos usando un formulario general (Formulario de Selección) y tras realizar la exploración clínica pertinente (a ojo desnudo o con lupa), los datos de los pacientes que fueron diagnosticados de QA fueron recogidos en un formulario adicional detallado (Formulario de QA). Se realizó un análisis descriptivo de todas las variables recopiladas en el estudio.

El protocolo del estudio fue aprobado por el Comité de Ética de Pontevedra-Vigo-Ourense, España (número de protocolo 2015/582). Todos los pacientes firmaron un consentimiento informado antes de participar en el estudio.

El estudio estadístico fue realizado mediante el paquete estadístico SPSS 22.0 para Windows.

RESULTADOS

Se incluyeron 1250 pacientes en el estudio y 11 de ellos se negaron a participar o a firmar el consentimiento informado; por lo tanto, 1239 pacientes completaron el Formulario de Selección. Entre ellos, 410 pacientes fueron diagnosticados de QA y se obtuvieron datos completos de 408 pacientes.

La prevalencia de QA en la comunidad autónoma de Galicia en pacientes con edad igual o superior a 45 años fue 31,3%.

Los factores de riesgo significativos e independientes de QA tras la realización de un análisis multivariante fueron: edad ≥60 años (de 60 a 69 años: OR = 4,07, $p < 0,001$; de 70 a 79 años: OR = 6,4, $p < 0,001$; de 80 a 89 años: OR = 9,46, $p < 0,001$; mayores de 90 años: OR = 8,64, $p = 0,004$), fototipo II de Fitzpatrick (OR = 2,94), trabajo en exteriores durante más de 25 años (OR = 7,14) e historia previa de cáncer cutáneo no melanoma (CCNM) (OR = 1,75).

Tan solo 9,3% de los pacientes con QA habían utilizado fotoprotección labial el año previo. La mayoría de ellos (62,1%) habían usado solo un envase de fotoprotector labial en dicho período. Se observó una correlación estadísticamente significativa entre el uso de fotoprotección labial y los fototipos de Fitzpatrick I y II (p=0,039). Las otra variables analizadas (sexo, edad, trabajo en exteriores durante más de 25 años e historia previa de CCNM) no mostraron una asociación significativa con la fotoprotección labial.

En el presente estudio se describieron las distintas manifestaciones clínicas de QA y sus factores de riesgo asociados. La presencia de descamación y eritema se asociaron significativamente con consumo de alcohol y trabajo en exteriores durante más de 25 años. El sexo masculino fue un factor protector frente a la presencia de descamación y el hábito tabáquico presente o pasado fue un factor protector con respecto a la presencia de eritema. El aspecto moteado del labio se asoció significativamente con una historia previa de CCNM.

Se detectaron marcadores de daño actínico crónico, como queratosis actínicas y/o lentigos solares, en 73,5% de los pacientes con QA. Los fototipos I y II de Fitzpatrick y la edad > 65 años se correlacionaron tanto con la presencia de queratosis actínicas como de lentigos solares en los pacientes con QA, pero una historia previa de CCNM se relacionó solamente con la presencia de queratosis actínicas.

DISCUSIÓN

La prevalencia de QA en nuestro estudio fue 31,3%; este valor fue excedido tan solo por dos estudios previos, ambos realizados en poblaciones específicas ampliamente expuestas a la radiación solar en Brasil (pescadores y trabajadores en el rubro de la caña de azúcar), que mostraron una prevalencia de QA de 43,24% (16) y 39,6% (22), respectivamente.

La elevada prevalencia de QA en nuestro estudio puede estar en parte relacionada con el progresivo envejecimiento de la población gallega. Otra razón que puede asociarse a la alta prevalencia encontrada pudo haber sido la inclusión de estadios tempranos de la enfermedad, como la descamación o cambios de color persistentes, ambos presentes en la definición clínica de De Oliveira Ribeiro *et al.* (24). Esta definición no ha sido considerada en otros estudios de prevalencia de QA.

Tal como se mencionó previamente, la comparación entre los distintos estudios debe ser realizada con precaución, ya que todos tienen diseños diferentes y la mayoría no incluyen la definición clínica

de QA en la que se han basado para realizar el diagnóstico de sus pacientes.

Se encontró una correlación significativa entre la edad ≥ 60 años y la presencia de QA; además, el riesgo se incrementó significativamente a medida que la edad aumentaba. Aunque otras publicaciones mostraron que el envejecimiento está significativamente asociado con la QA (21,23,24), nuestro estudio es el primero en mostrar un aumento de la tendencia a presentar QA a medida que se incrementa la edad.

El trabajo en el exterior durante más de 25 años se asoció significativamente con la presencia de QA; esta correlación ya fue reportada por otros autores (16,20,21,24,25) y es consistente con el hallazgo previo (asociación a edad ≥ 60 años), ambos relacionados con altas dosis acumuladas de radiación solar.

Se encontró una correlación entre la presencia de QA y el fototipo II de Fitzpatrick. Este hallazgo es consistente con publicaciones previas que mostraron una elevada prevalencia de QA en individuos con piel clara, raza blanca o caucásicos (20-25). Nuestro estudio es el primero en analizar datos referentes al fototipo de Fitzpatrick, color de ojos y cabello de los pacientes con QA.

El haber sido diagnosticado previamente de un CCNM se asoció significativamente con la presencia de QA. Ningún estudio de prevalencia previo había reportado esta correlación. Este hallazgo es congruente, ya que tanto la QA como el CCNM, sobre todo el CE, tienen como principal factor de riesgo la exposición solar.

Tan solo un 9,3% de los pacientes con QA utilizaron fotoprotección labial el año previo. Nuestro estudio es el primero que describió y analizó este tipo de fotoprotección específica en individuos con QA.

Hemos descrito las diferentes manifestaciones clínicas de QA y sus posibles asociaciones con factores de riesgo y estas asociaciones no han sido reportadas previamente. La correlación significativa entre el aspecto moteado y una historia de CCNM tiene un interés especial, puesto que la idea de que un simple signo clínico pueda predecir un posible incremento de riesgo de CCNM tiene un gran potencial para su aplicación clínica, aunque se necesitan futuros estudios para confirmar esta hipótesis.

La descripción y al análisis de los factores de riesgo relacionados con la presencia de queratosis actínicas y lentigos solares en pacientes con QA no ha sido comunicad con anterioridad. La edad > 65 años y los fototipos I y II de Fitzpatrick se correlacionaron significativamente con la presencia de queratosis actínicas y lentigos solares en pacientes con QA y estas asociaciones son coherentes, puesto que la radiación ultravioleta es el factor de riesgo principal para el desarrollo de dichas lesiones; el haber padecido previamente un CCNM se relacionó solamente con las queratosis actínicas y no con los lentigos solares, confirmando la conocida correlación entre el CCNM (especialmente el CE) y las queratosis actínicas, que de hecho son consideradas CE *in situ*.

La elevada proporción de pacientes con QA que presentaron indicadores de daño actínico crónico (73,5%) induce a recomendar

que todos los pacientes con QA deben ser sometidos a una exploración dermatológica en busca de signos de daño actínico crónico y, a la inversa, se debe realizar una exploración clínica labial en todos los pacientes con daño actínico crónico.

CONCLUSIONES

1. La QA es una patología prevalente en la población de la comunidad autónoma de Galicia con edad igual o superior a 45 años.

2. Los pacientes con QA en la población del estudio tuvieron una edad promedio superior a 70 años y se observó un predominio en mujeres.

3. Los sujetos con edad igual o superior a 60 años, con fototipo II de Fitzpatrick, que habían trabajado en exteriores durante más de 25 años y con historia previa de CCNM tuvieron un riesgo superior de desarrollar QA.

4. En sujetos con edad igual o superior a 60 años el riesgo de desarrollo de QA se incrementó progresivamente con la edad.

5. La mayoría de pacientes con QA no realizaban fotoprotección labial y, cuando lo hicieron, esta fue insuficiente.

6. Solo los pacientes con QA y fototipo I y II de Fitzpatrick mostraron tendencia al uso de fotoprotección labial.

7. Se deben promover medidas educativas que insistan en la importancia de la fotoprotección labial, especialmente en poblaciones de alto riesgo.

8. El aspecto moteado del labio fue la única manifestación clínica asociada a una historia previa de CCNM.

9. Otros signos de daño actínico crónico, como queratosis actínicas y/o lentigos solares, fueron prevalentes en los pacientes con QA.

10. Los pacientes con QA con edad igual o superior a 65 años y con fototipo de Fitzpatrick I y II tuvieron un mayor riesgo de desarrollo de lentigos solares.

11. Los pacientes con QA con edad igual o superior a 65 años, con fototipo de Fitzpatrick I y II e historia de CCNM tuvieron un mayor riesgo de desarrollo de queratosis actínicas.

12. La enfermedad labial fue el motivo de consulta dermatológica en muy pocos pacientes con QA, lo cual indica una ausencia de conocimiento de la patología entre la población.

13. La exploración labial minuciosa debería ser obligatoria en todos los pacientes con daño actínico crónico.

2
RESUMO

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2. RESUMO

INTRODUCIÓN

A queilitis actínica (QA) é unha patoloxía que afecta principalmente ao bermellón do beizo inferior dando lugar a alteracións clínicas e patolóxicas. A QA considérase maioritariamente unha forma superficial de carcinoma espinocelular (CE) e o principal factor de risco no seu desenvolvemento é a exposición solar crónica (1).

QA é a denominación máis comunmente utilizada para describir esta entidade (2,3). O termo "QA" foi considerado inapropiado por algúns autores por dous motivos. En primeiro lugar, a palabra "queilitis" implica un proceso inflamatorio que non é o feito predominante na QA. Ademais, a palabra "actínica" deriva do grego *aktin* que significa raio, pero a QA asociouse tan só coa radiación solar e non con outro tipo de radiación. En segundo lugar, a QA foi probablemente utilizada por algúns dermatólogos para referirse a outros cambios orixinados pola radiación ultravioleta sobre o beizo como, por exemplo, a elastosis solar, a atrofia solar ou as telangiectasias. A pesar da súa imperfección, QA é o termo máis frecuentemente utilizado na literatura científica e por iso se elixiu para esta tese doutoral, xa que é necesario o uso de nomenclatura uniforme para manter unha comunicación óptima entre clínicos, cirurxiáns e patólogos en todo o mundo (2).

No ano 2005, a Organización Mundial da Saúde (OMS) acuñou o termo *potentially oral malignant disorders* para englobar lesións orais con predisposición a unha posible transformación maligna (4-6) e a QA estaba incluída entre elas.

A QA é considerada por moitos autores un CE superficial do beizo, do mesmo xeito que sucede coas queratoses actínicas na pel (1,3,7-10). Aínda que houbo moita especulación a este respecto, a taxa de progresión de QA a CE invasivo descoñécese, debido á ausencia de estudos prospectivos ben deseñados, con seguimento a longo prazo e con confirmación histolóxica sistemática. A semi-mucosa labial é ademais unha área de alto risco de localización dos CE invasivos polo seu potencial metastático (8,11,12) e, por tanto, é fundamental profundar na epidemioloxía da QA, considerada unha forma superficial de CE que pode eventualmente progresar a un CE invasivo.

O número de publicacións referentes á epidemioloxía da QA é realmente escaso (13-27). Os datos relacionados coa prevalencia da QA están baseados en estudos metodológicamente heteroxéneos, a maioría deles levados a cabo en poboacións específicas de Sudamérica e ningún deles é un estudo multicéntrico. A comparación dos resultados dos mesmos é difícil debido a varias razóns, entre elas a ausencia dunha definición única de QA, a posible inclusión doutras patoloxías inflamatorias ou neoplásicas distintas á QA, as diferentes idades e sexos dos suxeitos incluídos ou a análise non homoxénea de posibles factores de risco como o fototipo de Fitzpatrick, a exposición solar previa ou o consumo de alcol ou tabaco. A inxesta enólica e o hábito tabáquico relacionáronse co cancro da cavidade oral (28-30) e tamén co cancro de labio, especialmente naqueles pacientes afeitos a

deixar o cigarro sobre o beizo (31). A influencia do tabaco no desenvolvemento da QA é controvertida, pero ata a data non se estableceu unha relación causa-efecto (3), aínda que parece evidente que a exposición constante á calor xerada pola combustión dos cigarros pode agravar o aspecto da enfermidade en suxeitos expostos crónicamente á radiación solar (3,14,21,32). Por todo o anterior, a prevalencia publicada de QA nos distintos estudos ten un rango amplo que abarca desde un 0,9% (15) ata un 43,24% (16).

Tal como se mencionou previamente, a pesar de que a radiación solar é o principal factor de risco da QA, existe pouca evidencia en relación ao uso de fotoprotección específica dirixida á rexión labial. A aplicación de fotoprotección labial de forma adecuada é a primeira e principal medida para previr o desenvolvemento da QA (23,33-37); a pesar disto, prestouse pouca atención aos hábitos de fotoprotección dirixidos especificamente aos beizos (33,38,39) e existen moi poucos estudos nos que investigara esta cuestión (40-43).

As manifestacións clínicas asociadas á QA son a presenza de secura labial, tacto rugoso e descamación, e en ocasións poden aparecer pliegues marcados, fisuras ou erosións (8,44). De Oliveira Ribeiro *et al*. propuxeron os seguintes signos clínicos para establecer o diagnóstico de QA (24):

1. Descamación: presenza de escamas
2. Fisuras verticais: liñas que se estenden á dermis subxacente
3. Atrofia: depresión do beizo como resultado do adelgazamento da dermis ou epidermis

4. Eritema: cor vermello do beizo causado por vasodilatación
5. Manchas: cambio de cor da mucosa normal sen elevación ou depresión algunha
6. Aspecto moteado: presenza simultánea de parches eritematosos e esbrancuxados
7. Placa: lesión sólida, elevada de superficie plana > 1 cm de diámetro
8. Ulceración: disrupción do epitelio con exposición do tecido conectivo subxacente
9. Demarcación borrosa entre o bordo da semi- mucosa labial e a pel da cara

A palpación é un compoñente importante da exploración clínica e a QA asociouse cun tacto similar a un papel de lixa fino (2). A presenza de infiltración, erosión mantida no tempo, ulceración, sangrado, atrofia e a ausencia dun límite preciso da semi-mucosa poden ser indicadores de progresión a CE (1,9,32,36,37).

A QA normalmente descríbese como un cadro asintomático, pero algúns estudos describiron síntomas asociados; o 16,47% de pacientes con QA experimentaron dor nun estudo (20) e o 34,48% (44) e 24,7% (37) de pacientes con QA noutros dous estudos referiron ardor e proído, respectivamente.

A evidencia confirma que o aspecto clínico da QA ten unha escasa correlación co grao de displasia celular; aínda que a precisión

diagnóstica pode incrementarse coas novas técnicas de imaxe (como a dermatoscopia ou a microscopía confocal), segue sendo necesario un seguimento próximo destes pacientes e débese realizar unha biopsia das lesións sospeitosas para poder descartar un CE invasivo, que é o diagnóstico diferencial máis importante da QA (2,8,32,36,37,44,45).

Galicia é unha comunidade autónoma localizada no noroeste de España. A súa poboación total no ano 2016 foi 2.718.525 habitantes (Instituto Galego de Estatística, http:www.ige.eu), constituíndo a 5ª rexión máis poboada de España.

Un problema realmente importante ao que se enfronta a comunidade autónoma galega é o progresivo incremento etario da poboación. Suxeitos cunha idade superior aos 65 anos constituíron o 24,31% da poboación total no ano 2016, o 24,56% no ano 2017 e o 24,89% no ano 2018. O crecemento vexetativo da poboación galega neses anos foi -12.695, -13.517 e -15.833, respectivamente (Instituto Galego de Estatística, http:www.ige.eu). O envellecemento da poboación é un motivo de preocupación en tódolos países industrializados e, dentro de Europa, Galicia é unha das rexións coa maior taxa proxectada de dependencia por idade avanzada no ano 2050 (46).

XUSTIFICACIÓN DO ESTUDO

A epidemioloxía da QA foi escasamente analizada no pasado. A maior parte dos estudos publicados realizáronse en poboacións específicas de Sudamérica, maioritariamente en Brasil, pero non se dispón de estudos epidemiolóxicos multicéntricos e cun deseño prospectivo.

A exposición solar é o factor de risco máis importante para o desenvolvemento de QA. Con todo, existen moi poucos estudos en que analizaran os beneficios dunha fotoprotección labial específica, en comparación coas numerosas publicacións relativas á fotoprotección da pel. A escasa evidencia dispoñible mostra que a poboación xeral non adoita utilizar rutinariamente un fotoprotector dirixido á rexión labial.

As manifestacións clínicas da QA foron descritas en varios estudos, pero ningún deles fixo referencia aos factores de risco específicos relacionados con cada unha das formas clínicas de QA. Ademais, marcadores de dano actínico crónico como as queratoses actínicas ou os lentigos solares e as súas posibles correlacións non foron analizadas nos pacientes con QA.

Co fin de dar resposta a todo o exposto, deseñouse un estudo multicéntrico transversal nun país con predominio de poboación caucásica, para avaliar a prevalencia de QA, analizar os seus factores de risco e manifestacións clínicas e investigar o uso de fotoprotección específica nos beizos.

OBXECTIVOS

O obxectivo principal foi determinar a prevalencia de QA na comunidade autónoma de Galicia, España, na poboación con idade igual ou superior a 45 anos.

Os obxectivos secundarios foron: (1) describir os factores de risco de QA na poboación do estudo, (2) establecer o perfil clínico e epidemiolóxico dos pacientes con QA, (3) investigar os hábitos dos

pacientes relacionados coa fotoprotección labial e a súa asociación coa exposición solar, (4) describir as diferentes manifestacións clínicas da QA e os seus posibles factores de risco e (5) avaliar os marcadores de dano actínico e os seus factores de risco nos pacientes con QA.

MATERIAL E MÉTODOS

Deseñouse un estudo descritivo, transversal, multicéntrico na comunidade autónoma de Galicia, localizada no noroeste de España. Oito hospitais participaron no estudo e os datos dos pacientes foron recompilados prospectivamente desde o 12 de Xaneiro do ano 2016 ata o 31 de Xaneiro do ano 2017. Os pacientes ≥ 45 anos catalogados como "Primeira Visita" que acudiron á consulta xeral de Dermatoloxía de cada un dos dermatólogos investigadores foron consecutivamente recrutados unha vez á semana durante o período do estudo. Aqueles pacientes que non puideron entender ou contestar as cuestións relativas á súa historia clínica foron excluídos.

Os datos do estudo foron recompilados polos dermatólogos usando un formulario xeral (Formulario de Selección) e tras realizar a exploración clínica pertinente (a ollo espido ou con lupa), os datos dos pacientes que foron diagnosticados de QA foron recollidos nun formulario adicional detallado (Formulario de QA). Realizouse unha análise descritiva de todas as variables recompiladas no estudo.

O protocolo do estudo foi aprobado polo Comité de Ética de Pontevedra-Vigo-Ourense, España (número de protocolo 2015/582). Todos os pacientes asinaron un consentimento informado antes de participar no estudo.

O estudo estatístico foi realizado mediante o paquete estatístico SPSS 22.0 para Windows.

RESULTADOS

Incluíronse 1250 pacientes no estudo e 11 deles negáronse a participar ou a asinar o consentimento informado; por tanto, 1239 pacientes completaron o Formulario de Selección. Entre eles, 410 pacientes foron diagnosticados de QA e obtivéronse datos completos de 408 pacientes.

A prevalencia de QA na comunidade autónoma de Galicia en pacientes con idade igual ou superior a 45 anos foi 31,3%.

Os factores de risco significativos e independentes de QA tras a realización dunha análise multivariante foron: idade $\geq$ 60 anos (de 60 a 69 anos: OR = 4,07, $p < 0,001$; de 70 a 79 anos: OR = 6,4, $p < 0,001$; de 80 a 89 anos: OR = 9,46, $p < 0,001$; maiores de 90 anos: OR = 8,64, $p = 0,004$), fototipo II de Fitzpatrick (OR = 2,94), traballo en exteriores durante máis de 25 anos (OR = 7,14) e historia previa de cancro cutáneo non melanoma (CCNM) (OR = 1,75).

Tan só 9,3% dos pacientes con QA utilizaran fotoprotección labial o ano previo. A maioría deles (62,1%) usaran só un envase de fotoprotector labial no devandito período. Observouse unha correlación estatisticamente significativa entre o uso de fotoprotección labial e os fototipos de Fitzpatrick I e II (p=0,039). As outras variables analizadas (sexo, idade, traballo en exteriores durante máis de 25 anos e historia previa de CCNM) non mostraron unha asociación significativa coa fotoprotección labial.

No presente estudo describíronse as distintas manifestacións clínicas de QA e os seus factores de risco asociados. A presenza de descamación e eritema asociáronse significativamente con consumo de alcol e traballo en exteriores durante máis de 25 anos. O sexo masculino foi un factor protector fronte á presenza de descamación e o hábito tabáquico presente ou pasado foi un factor protector con respecto á presenza de eritema. O aspecto moteado do beizo asociouse significativamente cunha historia previa de CCNM.

Detectáronse marcadores de dano actínico crónico, como queratoses actínicas e/ou lentigos solares, en 73,5% dos pacientes con QA. Os fototipos I e II de Fitzpatrick e a idade > 65 anos correlacionáronse tanto coa presenza de queratoses actínicas como de lentigos solares nos pacientes con QA, pero unha historia previa de CCNM relacionouse soamente coa presenza de queratoses actínicas.

DISCUSIÓN

A prevalencia de QA no noso estudo foi 31,3%; este valor foi excedido tan só por dous estudos previos, ambos realizados en poboacións específicas amplamente expostas á radiación solar en Brasil (pescadores e traballadores no rubro da cana de azucre), que mostraron unha prevalencia de QA de 43,24% (16) e 39,6% (22), respectivamente.

A elevada prevalencia de QA no noso estudo pode estar en parte relacionada co progresivo envellecemento da poboación galega. Outra razón que pode asociarse á alta prevalencia atopada puido ser a inclusión de estadios temperáns da enfermidade, como a descamación

ou cambios de cor persistentes, ambos presentes na definición clínica de De Oliveira Ribeiro *et al.* (24). Esta definición non foi considerada noutros estudos de prevalencia de QA.

Tal como se mencionou previamente, a comparación entre os distintos estudos debe ser realizada con precaución, xa que todos teñen deseños diferentes, con análise non homoxénea dos factores de risco e a maioría non inclúen a definición clínica de QA na que se basearon para realizar o diagnóstico dos seus pacientes.

Atopouse unha correlación significativa entre a idade ≥ 60 anos e a presenza de QA; ademais, o risco incrementouse significativamente a medida que a idade aumentaba. Aínda que outras publicacións mostraron que o envellecemento está significativamente asociado coa QA (21,23,24), o noso estudo é o primeiro en mostrar un aumento da tendencia para presentar QA a medida que se incrementa a idade.

O traballo no exterior durante máis de 25 anos asociouse significativamente coa presenza de QA; esta correlación xa foi reportada por outros autores (16,20,21,24,25) e é consistente co achado previo (asociación a idade ≥ 60 anos), ambos relacionados con altas doses acumuladas de radiación solar.

Atopouse unha correlación entre a presenza de QA e o fototipo II de Fitzpatrick. Este achado é consistente con publicacións previas que mostraron unha elevada prevalencia de QA en individuos con pel clara, raza branca ou caucásicos (20-25). O noso estudo é o primeiro en analizar datos referentes ao fototipo de Fitzpatrick, cor de ollos e cabelo dos pacientes con QA, características que foron previamente

consensuadas polos investigadores en reunión previas ao inicio do estudo co fin de evitar a aparición de sesgos inter observador.

O ser diagnosticado previamente dun CCNM asociouse significativamente coa presenza de QA. Ningún estudo de prevalencia previo reportara esta correlación. Este achado é congruente, xa que tanto a QA como o CCNM, sobre todo o CE, teñen como principal factor de risco a exposición solar.

Tan só un 9,3% dos pacientes con QA utilizaron fotoprotección labial o ano previo. O noso estudo é o primeiro que describiu e analizou este tipo de fotoprotección específica en individuos con QA.

Describimos as diferentes manifestacións clínicas de QA e as súas posibles asociacións con factores de risco e estas asociacións non foron reportadas previamente. A correlación significativa entre o aspecto moteado e unha historia de CCNM ten un interese especial, posto que a idea de que un simple signo clínico poida predicir un posible incremento de risco de CCNM ten un gran potencial para a súa aplicación clínica, aínda que se necesitan futuros estudos para confirmar esta hipótese.

A descrición e a análise dos factores de risco relacionados coa presenza de queratoses actínicas e lentigos solares en pacientes con QA non foi comunicada con anterioridade. A idade > 65 anos e os fototipos I e II de Fitzpatrick correlacionáronse significativamente coa presenza de queratoses actínicas e lentigos solares en pacientes con QA e estas asociacións son coherentes, posto que a radiación ultravioleta é o factor de risco principal para o desenvolvemento das devanditas lesións; o padecer previamente un CCNM relacionouse

soamente coas queratoses actínicas e non cos lentigos solares, confirmando a coñecida correlación entre o CCNM (especialmente o CE) e as queratoses actínicas, que de feito son consideradas un CE *in situ*.

A elevada proporción de pacientes con QA que presentaron indicadores de dano actínico crónico (73,5%) induce a recomendar que tódolos pacientes con QA deben ser sometidos a unha exploración dermatolóxica en busca de signos de dano actínico crónico e, á inversa, débese realizar unha exploración clínica labial en tódolos pacientes con dano actínico crónico.

É preciso que tanto os clínicos como as autoridades sanitarias establezan e difundan medidas de prevención primaria e secundaria relativas á detección de signos de dano actínico crónico e cancro cutáneo, non soamente dirixidas á pel, senon tamén aos labios. Estas recomendacións son especialmente importante en poboacións de alto risco como son os pacientes de fototipos baixos con antecedentes de exposición importante á radiación solar.

CONCLUSIÓNS

1. A QA é unha patoloxía prevalecente na poboación da comunidade autónoma de Galicia con idade igual ou superior a 45 anos.

2. Os pacientes con QA na poboación do estudo tiveron unha idade media superior a 70 anos e observouse un predominio en mulleres.

3. Os suxeitos con idade igual ou superior a 60 anos, con fototipo II de Fitzpatrick, que traballaran en exteriores durante máis de 25 anos e con historia previa de CCNM tiveron un risco superior de desenvolver QA.

4. En suxeitos con idade igual ou superior a 60 anos o risco de desenvolvemento de QA incrementouse progresivamente coa idade.

5. A maioría de pacientes con QA non realizaban fotoprotección labial e, cando o fixeron, esta foi insuficiente.

6. Só os pacientes con QA e fototipo I e II de Fitzpatrick mostraron tendencia ao uso de fotoprotección labial.

7. Débense promover medidas educativas que insistan na importancia da fotoprotección labial, especialmente en poboacións de alto risco.

8. O aspecto moteado do beizo foi a única manifestación clínica asociada a unha historia previa de CCNM.

9. Outros signos de dano actínico crónico, como queratoses actínicas e/ou lentigos solares, foron prevalecentes nos pacientes con QA.

10. Os pacientes con QA con idade igual ou superior a 65 anos e con fototipo de Fitzpatrick I e II tiveron un maior risco de desenvolvemento de lentigos solares.

11. Os pacientes con QA con idade igual ou superior a 65 anos, con fototipo de Fitzpatrick I e II e historia de CCNM tiveron un maior risco de desenvolvemento de queratoses actínicas.

12. A enfermidade labial foi o motivo de consulta dermatolóxica en moi poucos pacientes con QA, o cal indica unha ausencia de coñecemento da patoloxía entre a poboación.

13. A exploración minuciosa dos beizos debería ser obrigatoria en tódolos pacientes con dano actínico crónico.

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3
ABSTRACT

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3. ABSTRACT

INTRODUCTION

Actinic cheilitis (AC) is an abnormal condition of the lower lip and is considered a superficial form of squamous cell carcinoma (SCC). Chronic sun exposure is the main risk factor for the development of AC.

Evidence shows that the clinical appearance of AC correlates poorly with the degree of cellular dysplasia; this means that even when accuracy of diagnosis can be increased with new imaging techniques (such as dermoscopy and confocal microscopy), it is necessary to biopsy suspicious lesions to rule out invasive SCC, the most important differential diagnosis of AC.

The actual rate of progression of AC to invasive SCC has not been established, but because SCC on the lip is considered a high-risk location, analysing the risk factors of AC is imperative for preventing invasive SCC. As stated above, even though solar radiation is the main risk factor for AC, there is little evidence regarding specific lip photoprotection.

The prevalence of AC in Europe is unknown to date. Some epidemiological studies on AC have been conducted in specific populations primarily in Brazil, South America, but comparing their

results is difficult owing to their heterogeneous design and the absence of a uniform definition of AC. Specific lip photoprotection has been poorly analysed in the past. The clinical presentation of AC has been described in various studies, but the possible association between its clinical manifestations and risk factors has not been reported to date. Further, actinic damage markers in AC patients have not been analysed.

To address this knowledge gap, we designed a cross-sectional multi-centre study in a Western country with a predominantly Caucasian population to assess the prevalence of AC, analyse its risk factors and clinical manifestations, and investigate the use of specific lip photoprotection.

OBJECTIVES

We primarily aimed to determine the prevalence of AC in the Galicia region of Spain.

Our secondary objectives were to: (1) describe the risk factors of AC in our study population, (2) establish the clinical and epidemiological profile of AC patients, (3) investigate patient habits regarding lip photoprotection and their association with sun exposure, (4) describe the different clinical manifestations of AC and their possible risk factors and (5) assess the markers of actinic damage in our AC patients along with their risk factors.

MATERIALS AND METHODS

A cross-sectional multi-centre study was conducted in the Galicia region of north-western Spain. The dermatology departments of 8 institutes participated in the study and patient data were collected prospectively from 12th January 2016 to 31st January 2017.

"First-visit" patients aged ≥45 years who visited the general dermatology outpatient clinics were consecutively recruited once a week during the study period. Patients who were not able to understand or answer questions regarding their clinical history were excluded.

Data were collected by the dermatologists using a general form (Screening Form) and after performing clinical examinations (naked eye and/or magnifying glasses), data from patients diagnosed with AC were collected in an additional detailed questionnaire (AC Form). A descriptive analysis was performed for all the collected variables.

The study protocol was approved by the Research Ethics Committee of Pontevedra-Vigo-Ourense, Spain (protocol number 2015/582). All patients provided informed consent before being enrolled in the study.

All statistical analyses were performed using the SPSS 22.0 statistical software for Windows.

RESULTS

We enrolled 1,250 patients in the study, 11 of whom declined to participate or sign the consent form; therefore, 1,239 patients completed the Screening Form. Of these, 410 patients had AC and we obtained complete data for 408 patients.

The prevalence of AC in the Galician population aged 45 years and older was 31.3%, almost one-third of the population of the study. The significant and independent risk factors of AC after our multivariate analysis were: age of ≥60 years, Fitzpatrick skin phototype II, outdoor occupation for >25 years and history of non-melanoma skin cancer (NMSC).

Only 9.3% of the AC patients used lip photoprotection balms. A majority of them (62.1%) had used only one stick in the previous year. We observed a statistically significant correlation between the use of lip sunscreen and Fitzpatrick's phototypes I and II (p = 0.039). The other variables we analysed (sex, age, working outdoors for > 25 years, and a history of NMSC) did not show any significant association with lip sun protection.

We described the different clinical manifestations of AC and their associated risk factors. Notably, mottled lip appearance was significantly associated with a history of NMSC and this correlation has not been reported in the literature previously.

We detected markers of chronic sun exposure, such as actinic keratosis (AK) and/or lentigines, in 73.5% of patients with AC. Both Fitzpatrick skin types I and II and age of >65 years correlated with

AK and lentigines in AC patients, whereas a history of NMSC was related only to AK. This confirms the known correlation between NMSC, especially SCC, and AK.

CONCLUSIONS

1. AC is a prevalent condition in the Galician population among individuals aged 45 years and older.

2. Patients affected by AC in this population had an average age over 70 years and women were prevailing.

3. Subjects who were aged 60 years and older, had Fitzpatrick skin phototype II, had worked outdoors for >25 years and had a history of NMSC were at a higher risk of developing AC.

4. In subjects aged 60 years and older the risk of developing AC increased greatly with age.

5. The majority of AC patients did not practice lip photoprotection and even when they did, it was insufficient.

6. Only AC patients with Fitzpatrick's skin types I and II tended to use lip sun protection.

7. Promoting educational and preventive measures to address the importance of lip protection among the public will be beneficial, especially in high-risk populations.

8. Mottled appearance was the only clinical manifestation of AC that was significantly associated with a history of NMSC.

9. Other signs of actinic damage, such as AK and/or lentigines, were prevalent among AC patients.

10. AC patients aged 65 years and older and with Fitzpatrick skin phototypes I and II were at a higher risk of developing lentigines.

11. AC patients aged 65 years and older with Fitzpatrick skin phototypes I and II and a history of NMSC were at a higher risk of suffering from AK.

12. Very few subjects with AC sought dermatological advice regarding their lips, indicating a lack of concern regarding AC in the population.

13. Careful lip examination should be made mandatory for all patients with chronic actinic damage.

4

INTRODUCTION

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4. INTRODUCTION

Actinic cheilitis (AC) is a condition that mainly affects the vermillion of the lower lip, causing clinical and histological changes as a result of chronic sun exposure (1).

4.1 TERMINOLOGY

AC is the most common name of this entity, but other acceptable terms include actinic cheilosis, actinic keratosis, solar cheilosis or solar keratosis (2,3).

The term “AC” has been considered inadequate because of two reasons. Firstly, AC does not indicate the true nature of the process; “cheilitis” implies an inflammatory condition of the lips that may affect the underlying connective tissue, but inflammation is not the main feature in AC. The term “actinic” is derived from the Greek word *aktin*, which means “ray”, but AC is only associated with solar radiation and not all types of radiation. Secondly, AC has probably been used by some dermatologists to report other actinically induced changes in the lower lip, such as solar elastosis, solar atrophy or solar telangiectasias (1,3).

Despite this imperfection, AC continues to be the most frequently reported term in the literature. Therefore, we have written “AC” in this doctoral dissertation because using uniform

nomenclature is mandatory for maintaining optimal communication between clinicians, surgeons and pathologists worldwide (2).

4.2 NATURE OF AC

In 2005, the World Health Organization (WHO) coined the term "potentially oral malignant disorders" to classify oral lesions that predisposed to malignant transformation in order to promote uniform reporting (4-6). These lesions included leukoplakia, erythroplakia, lichen planus, oral submucous fibrosis, and several miscellaneous disorders, including AC.

Many authors considered AC to be a superficial form of squamous cell carcinoma (SCC) of the lip that was similar to actinic keratosis (AK) (1,3,7-10). To date, the rate of progression of AC to invasive SCC has not been established because of a lack of well-designed, prospective, long-term follow-up studies with systematic histological confirmation of AC.

The vermillion border of the lip is a high-risk area for invasive SCC due to its high metastatic potential (8,11,12); therefore, clinicians need to gain knowledge about the epidemiology of AC, a superficial and incipient form of SCC that may eventually evolve to an invasive cancerous condition.

4.3 EPIDEMIOLOGY

There have been few epidemiological studies of AC prevalence compared to those related to AK (13-27). The current data on AC

prevalence are based on methodologically heterogeneous studies, most of which were performed in specific populations (primarily in South America) and none of them is a multi-centre study. Comparing the results of these studies is difficult because of several reasons. First, there is no unified definition of AC among them. Second, some studies may have included other inflammatory or neoplastic conditions of the lip, such as contact cheilitis or even invasive SCC in their analysis. Third, the age of inclusion differs among the publications; some included patients of all ages (16-18,20-22,24-26) while others included individuals older than a specific age (e.g., 14 years onwards (27) to older than 65 years (15)). Fourth, few studies only sampled male patients (14,17), whereas the rest included both males and females. Fifth, the previously reported AC risk factors, such as Fitzpatrick's skin type, solar exposure and tobacco or alcohol consumption were included unequally. A summary of the different prevalence studies in general and specific populations is presented in Table 1.

We did not research retrospective studies performed in dental or oral hospitals or retrospective analyses of histopathologic samples of different oral diseases because the design of these studies is different from ours, and they cannot be used to determine AC prevalence because they sampled patients with a previous oral pathology, which could create a selection bias in our study.

Table 1: AC prevalence studies and principal characteristics related to AC population.

Author	Number of patients (n)	Type of population	Population age	Population sex	AC prevalence	AC population age	AC population sex	Phenotype	Solar exposure	Tobacco consumption	Alcohol consumption
Jorge Junior J *et al.* (13)	270	Institutionalize elderly individuals	US	49.63% males; 50.37% females	2.6%	NA	NA	NA	NA	NA	NA
Campisi G *et al.* (14)	118	General population of Pantelleria (Sicilly)	≥ 40 years	Males only	4.6%	NA	Males only	NA	All outdoors workers	Correlation between AC and tobacco smoking+ alcohol drinking	
Espinoza I *et al.* (15)	889	General population	> 65 years	Both sexes	0.9%	NA	NA	NA	NA	NA	NA
Silva FD *et al.* (16)	111	Fisherman in Santa Catarina State, Brazil	Any age	Both sexes	43.24%	NA	NA	NA	Correlation with higher cumulated dose	No correlation	No correlation
Burke WA *et al.* (17)	81	Fishermen in North Carolina	Any age	Males only	15%	NA	Males only	All type II	NA	NA	NA
Zanetti R *et al.* (18)	420	General population in Campinas City, Brazil	Any age	Both sexes (48.81% males; 51.19% females)	18.1%	NA	69.7% males, 30.3% females	73.7% Caucasians	46.1% exposed during work; 36.8% exposed during leisure; 28.6% exposed during sport activities	NA	NA
Henrique PR *et al.* (19)	1006	Uberaba City, Minas Gerais, Brazil	> 20 years	Both sexes	2.4%	NA	NA	NA	NA	NA	NA
Miranda AMO *et al.* (20)	1539	Sugarcane workers in Brazil	Any age (mean age = 34.56 years)	Both sexes (63.54% males, 36.46% females)	9.6%	Mean age 37.4 years	Correlation with male sex	Correlation with Caucasians	Correlated with sun exposure > 10 years	No correlation	NA

Author	Number of patients (n)	Type of population	Population age	Population sex	AC prevalence	AC population age	AC population sex	Phenotype	Solar exposure	Tobacco consumption	Alcohol consumption
Martins-Filho PR *et al.* (21)	240	Farmers in northeastern Brazil	Any age	Both sexes	16.7%	Correlation with age ≥ 50 years	Correlation with male sex	Correlation with fair skin	Daily exposure > 8 hours	No correlation	NA
Junqueira JL *et al.* (22)	202	Sugarcane workers in southeast Brazil	Any age	Both sexes	39.6%	No correlation with age	No correlation with gender	Correlation between being black or mulatto with lower risk of AC	No correlation because all workers were exposed 7 hours/day for 5 days/week	No correlation	Positive correlation with AC development
De Souza Lucena EE *et al.* (23)	362	Beach workers in northeast Brazil	> 37 years	Both sexes	15.5%	Correlation with age ≥ 37 years	Correlation with male sex	Correlation with light skin	No correlation	No correlation	No correlation
De Oliveira Ribeiro A *et al.* (24)	201	Fishermen and women in Serpige, Brazil	Any age	Both sexes	11.4%	Correlation with age ≥ 50 years	No correlation with gender	Correlation with fair skin	Correlation with cumulative exposure of ≥ 30 years and with daily exposure of ≥ 4 hours	No correlation	NA
Gheno JN *et al.* (25)	801	Agribusiness show in Esteio city, Brazil	Any age	Both sexes	25.5%	NA	Correlation with male sex	Correlation with white people	Correlation with higher amount of sun exposure	No correlation	No correlation
Silva MF *et al.* (26)	51	Diabetic type 1 and 2 population in Brazil	Any age	Both sexes	13.7%	NA	NA	NA	NA	NA	NA
Ferreira AM *et al.* (27)	1385	Rural workers in northeast Brazil	≥ 14 years	Both sexes	28.4%	NA	NA	NA	NA	NA	NA

NA: Not analysed, US: Unspecified, Red text: Statistically significant correlation found.

The published prevalence of AC ranges from 0.9% (15) to 43.24% (16). This wide range is probably because of the above-mentioned non-uniform, heterogeneous definition of AC, the absence of cross-sectional multi-centre studies and the differences among the analysed populations.

Two studies reported a statistically significant correlation between AC and the age of ≥ 50 years (21,24) while another study found that AC correlated significantly with individuals aged ≥37 years (23). A study on Brazilian sugar-cane workers found no significant differences among three defined age groups (<35 years, 35–45 years, and >45 years) (22). The remaining studies did not investigate a possible correlation between age and AC prevalence.

Among the studies that considered both sexes for analysis, four found a significant correlation between AC and male subjects (20,21,23,25).

All studies that investigated skin colour found a significant correlation between fair/light/white skin and higher AC prevalence (20-25). Only one of these studies used Fitzpatrick's skin-type classification (17), showing that all the patients with AC had a type II of the mentioned classification.

Previous solar exposure was not analysed in all the studies, despite it being the main risk factor of AC. In those that did investigate it, the analyses were not uniform; some investigators found a correlation with years of cumulated exposure (20,24), some with daily exposure (21,24), and others with "high" (16) or "great" (25) exposure.

In general, tobacco consumption and alcohol intake are related to oral cancer (28-30) and lip cancer, especially in patients who are habituated to leaving the cigarette on their lips while smoking (31). The influence of smoking on the development of AC is controversial, but a causative relationship between them has not been established (3), even though it is evident that constant exposure to the heat generated by smoke combustion may aggravate the disease in individuals who are also exposed to solar radiation (3,21,24,32). A few studies that investigated the relationship between tobacco consumption and AC found no significant correlation between them (16,20-22), except Campisi & Margiota (14), who reported in 5 patients with AC a significant association with both tobacco smoking and alcohol drinking, but not separately.

Alcohol consumption was correlated with AC in one study (22) similar to the aforementioned study by Campisi & Margiota (14), but the daily/weekly intake was not specified. Three studies found no association between alcohol and AC (16,23,25). This correlation was not analysed in the remaining studies (13,15,17-21,24,26,27).

4.4 AC, SOLAR EXPOSURE AND PHOTOPROTECTION

The anatomical upright position of the lower lip makes it susceptible to a large amount of UV radiation, which is why AC frequently develops on the lower vermillion of the lip.

Adequate photoprotection is recommended as the first and most important measure to prevent AC (23,33-37); however, little attention has been paid to sun protection habits specifically for the lips (33,38,39) with very few studies investigating this issue.

The role of lip photoprotection in decreasing the risk of lip cancer was revealed in a case-control study on Californian women, which showed that the risk of lip cancer doubled in women who applied lip sun protection infrequently (no more than once a day) (40).

In a survey of 299 beachgoers in Texas on skin and lip photoprotection, subjects with Fitzpatrick's phototypes I to III were more likely to use sunscreen for skin protection than subjects with types IV to VI, however, the use of specific lip protection was not higher in phototypes I to III. This study also observed that lip sunscreen was used significantly more by women than men (41).

De Souza Lucena *et al.* studied 362 beach workers in north-eastern Brazil and found that working outdoors was the only factor that was associated with the use of any type of photoprotection (both skin and lip-specific). The proportion of workers who used a lip sunscreen was only 14% (42).

Another study investigated compliance with sunscreen advice in 4837 adult skiers and snowboarders in high-elevation skiing areas (43). Complete compliance with photoprotection measures was less overall (4.4% of the responders), but it was higher among those who also used a sunscreen lip balm, reflecting that a small group of people were aware of the complete protocol that included both skin and lip protection.

Although solar exposure is established as the main risk factor for AC (and subsequently, SCC) the limited number of previous studies led us to conclude that lip photoprotection has not been as widely studied as skin protection has; however, even this scarce

evidence shows that specific lip photoprotection is carried out as a habit only by a minority of the studied populations.

4.5 Clinical manifestations of AC

AC causes dry, rough and scaly lips that may sometimes have marked folds, fissures or erosions (8,44). Early signs of AC, such as dryness or desquamation, are also characteristic of normal ageing of the skin and are often overlooked by patients (44).

De Oliveira Ribeiro proposed the following signs to diagnose AC (24):

1. Scaling: the presence of flakes or plates caused by the desquamation of the stratum corneum
2. Vertical fissures: linear cleavages extending into the dermis
3. Atrophy: depression of the lip resulting from thinning of the dermis or epidermis
4. Erythema: reddening of the lip caused by vasodilatation
5. Spotting: change of colour of the normal mucosa without any elevation or depression
6. Mottled appearance: the simultaneous presence of erythematous and white patches
7. Plaque: a solid, raised, flat-topped lesion >1 cm in diameter
8. Ulceration: disrupted epithelium with exposed underlying connective tissue

9. Blurred demarcation between the vermilion border of the lip and the skin of the face.

AC has been described as a predominantly single lesion by some authors (2,8), while others have reported it as a multifocal disease (21,36).

As mentioned above, the lower lip is by far the most commonly affected area due to the direct incidence of UV radiation, and for the same reason, the vermillion surface is more affected than the angular area of the lips (8).

Da Silva *et al.* proposed a classification of AC based on the severity of its clinical manifestations (16): (1) mild/initial lesions: dryness and desquamation, (2) moderate lesions: severe dryness, desquamation, and presence of fissures, and (3) severe lesions: all the above along with infiltration, loss of delimitation between the vermillion border and adjacent skin, ulcers and crusting.

Palpation is an important component of the diagnosis; a fine sandpaper-like feeling is usually associated with AC (2). Infiltration, sustained erosion or ulceration, bleeding, atrophy, and the absence of a distinct vermillion border can also indicate impending SCC (1,9,32,36,37).

AC is usually described as an asymptomatic condition, but a few studies have reported symptoms; 16.47% of AC patients in one study experienced pain (20), and 34.48% (44) and 24.7% of AC patients (37) in two other studies reported burning and itching, respectively.

Clinically differentiating AC from early invasive SCC is difficult because there is no correlation between the clinical findings and the histopathological grade of dysplasia; therefore, repeated biopsies and close follow-ups are highly recommended (2,8,32,36,37,44,45).

4.6 CHARACTERISTICS OF THE GALICIA REGION

Galicia is a region located in northwest Spain. Geographically, it is bordered by the Atlantic Ocean to the west, the Cantabrian Sea to the north, the Asturias and Castilla-Leon regions to the east and Portugal to the south.

Galicia has a total area of 29,574 km^2 and the total population in 2016 was 2,718,525 (Galician Statistics Institute, http://www.ige.eu), making it the 5th most populated region in Spain.

As of 2017, the economy of Galicia was distributed among sectors in terms of gross market value as tertiary sector = 66.8%, secondary sector = 27.4%, and primary sector = 5.8% (Eurostat, 2019). The tourism, metallurgical and particularly fashion sectors are major players in Galicia's economy.

A major demographic problem in Galicia is the progressively increasing age of the population. Individuals aged above 65 years accounted for 24.31% of the total population in 2016, 24.56% in 2017 and 24.89% in 2018; the population growth in these years was -12,695, -13,517, and -15,833, respectively (Galician Statistics Institute, http://www.ige.eu). Ageing is a major public health concern

in industrialized countries and across Europe, Galicia is one of the European regions with the highest projected old-age dependency ratio by 2050 (46).

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5

RATIONALE OF THE STUDY

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5. RATIONALE OF THE STUDY

AC has been poorly analysed as compared with its widely studied skin counterpart, AK. So far, specific populations in South America have been studied, but there is a lack of well-designed, multi-centre, prospective studies on the epidemiology of AC.

Solar exposure is established as the main risk factor for the development of AC; however, studies investigating the benefits of specific lip photoprotection are scarce as compared with studies on skin protection. The few published evidence shows that the general population does not tend to practice lip protection against UV radiation.

The clinical manifestations of AC have been described in many studies; however, to date, none of them have explained specific risk factors for different clinical forms of AC. Markers of actinic damage, such as AK or lentigines and their possible correlations, have not been previously analysed in AC patients.

AC is considered a superficial form of SCC and can evolve into invasive SCC. In light of this risk, we aimed to add to the present literature by designing a cross-sectional, multi-centre prevalence study in a Western country with a predominantly Caucasian population to analyse the risk factors, clinical manifestations, associated markers of actinic damage and the use of specific lip photoprotection in patients with AC.

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6

OBJECTIVES

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6. OBJECTIVES

6.1 MAIN OBJECTIVE

- To determine the prevalence of AC among individuals aged ≥45 years in the Galicia region of north-western Spain

6.2 SECONDARY OBJECTIVES

- To describe the risk factors for AC in the study population
- To establish the clinical and epidemiological profile of patients with AC
- To determine lip photoprotection habits in AC patients and study the associated demographic and clinical variables
- To describe the different clinical manifestations of AC and their association with respective risk factors
- To study the association between AC and other markers of actinic damage

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7

MATERIALS, METHODS AND RESULTS

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7. MATERIALS, METHODS AND RESULTS

A detailed description of the materials, methods and results of the research have been published in scientific articles in three independent publications that are cited as follows:

1. Rodríguez-Blanco I, Flórez Á, Paredes-Suárez C, Rodríguez-Lojo R, González-Vilas D, Ramírez-Santos A, Paradela S, Suárez Conde I and Pereiro-Ferreirós M. Actinic cheilitis prevalence and risk factors: A cross-sectional multicentre study in a population aged 45 years and over in northwest Spain. Acta Dermato-Venereologica 2018;98(10):970-4 (47).

   Last impact factor available (2019): 4.016

   Impact factor in the year of publication (2018): 3.531.

   Rank position 13/66, Q1.

2. Rodríguez-Blanco I, Flórez Á, Paredes-Suárez C, Rodríguez-Lojo R, González-Vilas D, Ramírez-Santos A, Paradela S, Suárez Conde I and Pereiro-Ferreirós M. Use of lip photoprotection in patients suffering from actinic cheilitis. European Journal of Dermatology 2019;29(4):383-6 (48).

   Impact factor in the year of publication (2019): 2.782

   Rank position 23/68, Q2.

3. Rodríguez-Blanco I, Flórez Á, Paredes-Suárez C, Rodríguez-Lojo R, González-Vilas D, Ramírez-Santos A, Paradela S, Suárez Conde I and Pereiro-Ferreirós M. Actinic cheilitis: Analysis of clinical subtypes, risk factors, and associated signs of actinic damage. Acta Dermato-Venereologica 2019;99(10):931-2 (49).

   Impact factor in the year of publication (2019): 4.016.

   Rank position 7/68, Q1.

   I declare that I contributed to the design, analysis and interpretation of data of the mentioned publications, I have drafted them and revised them critically ensuring that the accuracy and integrity of any part of the work were appropriately investigated in order to achieve the final version of each of the published articles.

8

DISCUSSION

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8. DISCUSSION

Cross-sectional studies are characterised by the collection of relevant information at a given point in time. They are useful in assessing the prevalence of a disease and consequently, the burden of that disease on a population. Cross-sectional studies can be based on whole-population data obtained from national registries or on representative samples of a population (50).

In the present study, a sample of the Galician population was selected by 8 dermatology consultants from 8 different hospitals. Individuals with any skin problem who sought advice from a dermatologist were selected for the study. Consecutive patients attending a general dermatology outpatient clinic were recruited once a week for approximately one year. Only "first-visit" patients aged ≥ 45 years were enrolled (47).

The AC prevalence in our study was 31.3%; this value was exceeded by two previous studies, both of which included specific sun-exposed populations in Brazil (fishermen and sugar-cane workers) and showed prevalence values of 43.24% (16) and 39.6% (22). The high prevalence rate found in our study, almost one third of the Galician population ≥45 years, could be partly related to the increasing median age of Galicia. In 2016, individuals aged 65 and older accounted for 24.31% of the total Galician population (Galician Statistics Institute, http://www.ige.eu) making it one of the regions

with the highest projected old-age dependency ratio by 2050 in Europe (46).

Another reason for our high prevalence rate could be the inclusion of early stages of the condition, such as persistent desquamation or persistent colour changes, according to the clinical definition of AC given by De Oliveira Ribeiro *et al.* (24). However, this definition has not been considered in other studies.

As mentioned above, comparisons between different studies must be made with caution since they are all differently designed and most of them have not mentioned the clinical definition of AC as per which they diagnosed their patients (13-15,17-19,22,23,25-27).

In our study, the significant and independent risk factors of AC after multivariate analysis were: patients aged ≥ 60 years, working outdoors for more than 25 years, a Fitzpatrick skin phototype II and a previous history of non-melanoma skin cancer (NMSC) (Fig. 1).

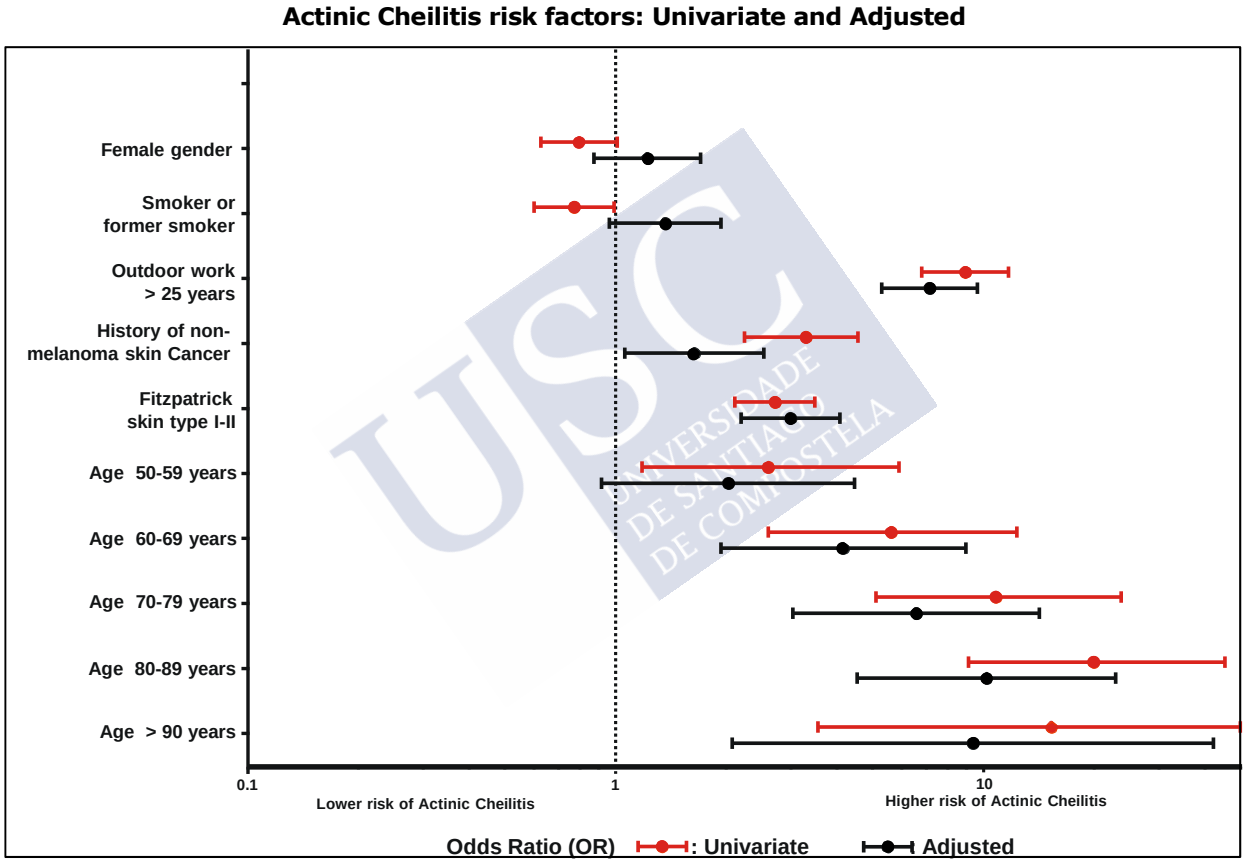

Figure 1: The univariate and adjusted risk factors of actinic cheilitis.

We found a significant and independent correlation between a patient age of ≥ 60 years and AC; the risk increased significantly with age (from 60 to 69 years: OR = 4.07, $p < 0.001$; from 70 to 79 years: OR = 6.4, $p < 0.001$; from 80 to 89 years: OR = 9.46, $p < 0.001$; older than 90 years: OR = 8.64, $p = 0.004$) (Fig. 2). As mentioned above, other studies have shown that ageing is significantly associated with AC (21,23,24), but our study is the first to illustrate a high tendency to AC risk with an increase in age.

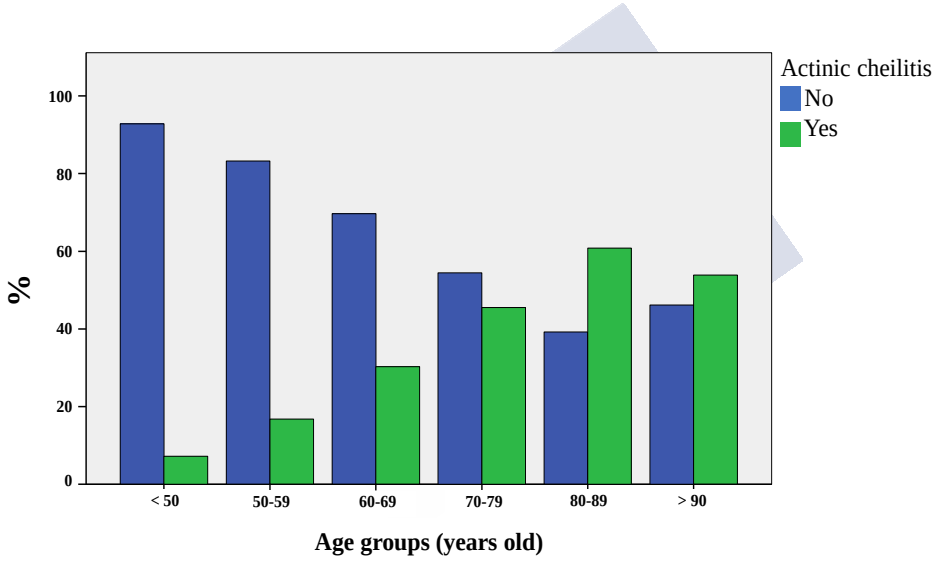

Figure 2: Increase of AC risk in relation to age.

* Compared with an age group of <50 years and adjusted for sex, skin phototype, outdoor working, tobacco consumption and history of NMSC.

Patients who had worked outdoors for more than 25 years were significantly associated with AC prevalence (OR = 7.14). This correlation has been reported by other authors (16,20,21,24,25) and is consistent with our previous finding (age ≥ 60 years); both are related to high doses of cumulative actinic radiation (Fig. 3).

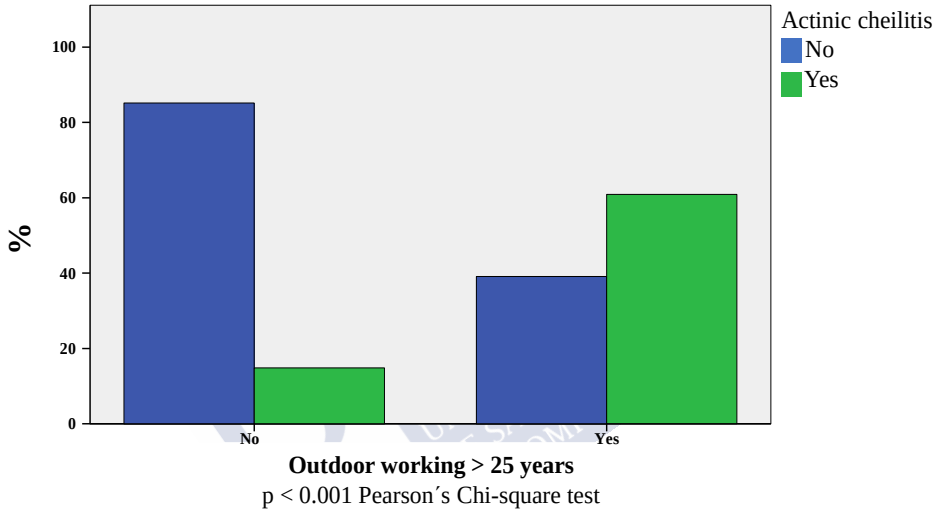

Figure 3: Occurrence of AC in relation to outdoor working for > 25 years.

We found a significant correlation between the occurrence of AC and Fitzpatrick phototype II (OR = 2.94) (Fig. 4), which is consistent with previous studies that revealed high AC prevalence rates in light/fair-skinned individuals or those who were white or Caucasian (20-25). Our study is the first to report data regarding the Fitzpatrick phototype, eye, and hair colour of AC patients.

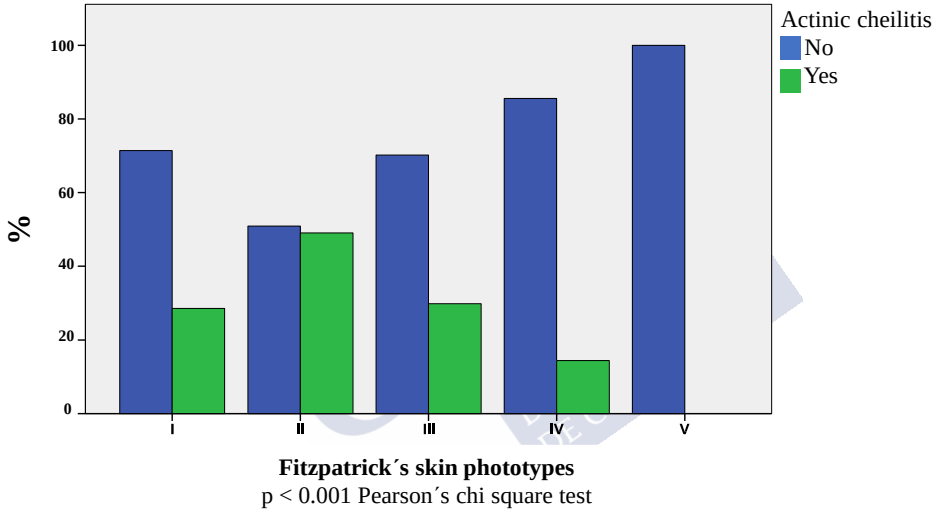

Figure 4: Presence of AC in relation to Fitzpatrick´s skin phototype.

A previous history of NMSC was significantly associated with AC (OR = 1.75). No previous AC prevalence studies have reported this correlation (Fig. 5). Our finding is consistent, as both AC and NMSC, mainly SCC, share solar exposure as a critical risk factor.

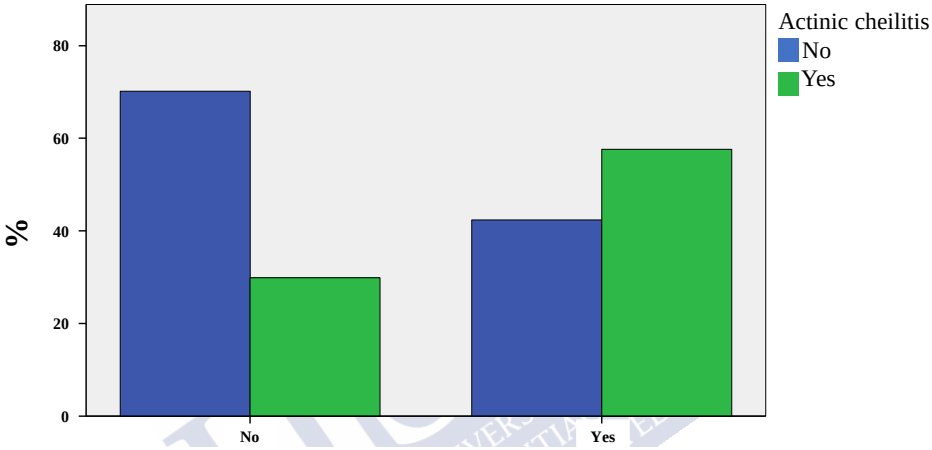

Figure 5: History of NMSC in relation to the occurrence of AC.

Our study population displayed a history of different types of NMSC: 59% had basal cell carcinoma (BCC), 35.9% had SCC and 5.1% presented with both lesions (Fig. 6). Of the 32 patients with a previous history of SCC, only 2 (6.3%) had lip lesions.

The prevalence of AC in our study was not significantly correlated with either gender, alcohol or tobacco consumption.

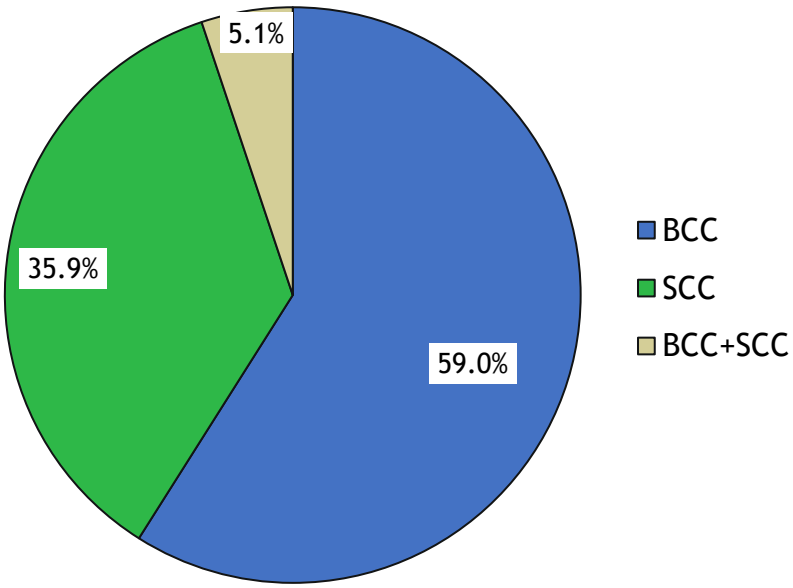

Figure 6: Types of NMSC in the AC patient population.

Only 9.3% of our AC subjects used lip photoprotection; among them, those who sometimes, almost always and always used a lip sunscreen were 6.1%, 2.2%, and 1%, respectively (Fig. 7). The only variable that was significantly associated with the use of lip photoprotection was Fitzpatrick's phototypes I and II (p = 0.039). Even though women protected their lips from UV radiation more than men, the difference was not significant (p = 0.090). The remaining variables we analysed (age, working outdoors for >25 years, and a history of NMSC) did not show any significant correlations.

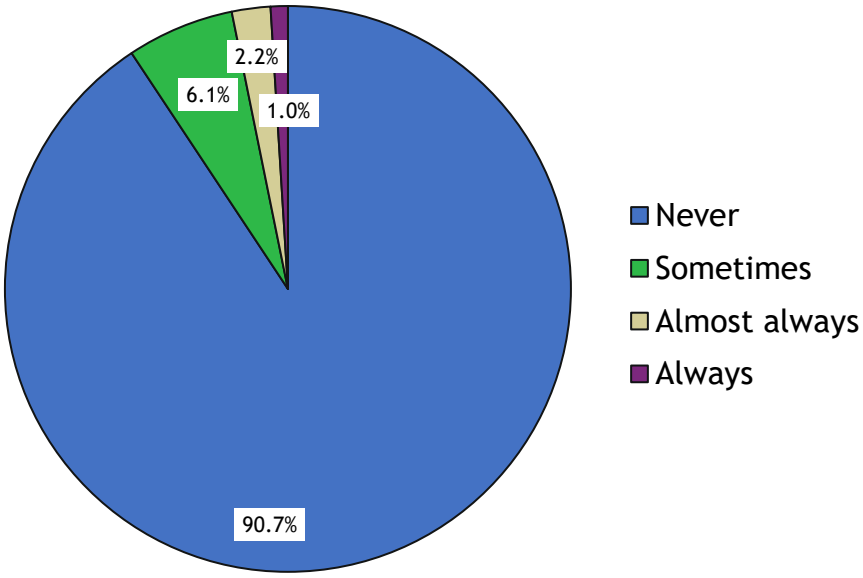

Figure 7: Use of lip photoprotection among AC patients.

As mentioned above, specific lip photoprotection has been poorly analysed in the past. To address this knowledge gap, we thoroughly reviewed the previous AC prevalence studies (Table 2). In contrast to the general view of AC being prevented with lip protection, Lucena *et al.* found a statistically significant correlation between the occurrence of AC and the use of sunscreen with a cap/hat, indicating that those using these photoprotection measures were more likely to develop AC. The authors considered that this could be due to the use of short-brimmed hats that did not offer protection on the lower part of the face, giving their subjects a false perception of protection, such that they did not feel the need to use sunscreens or lip protectors (23). Other prevalence studies showed a variety of results; Silva *et al.* investigated the prevalence of lip diseases in fishermen from Santa Catarina Island and found no association between the use of general sun protection (hat/cap, sunscreen) and prevalence of AC; however, they did report a statistically significant correlation between the use of sunscreen (not specifically lipstick) and a lower prevalence of AC (16). A study on farmers in northeast Brazil showed that their habit of using a cloth to cover the face and applying sunscreen was associated with a lower number of AC cases (21). Another study in Brazil found a significant correlation between the non-use of sunscreens and the development of AC in a population of fishermen and fisherwomen (24). AC was negatively associated with the use of hats in other studies, but specifications related to the type or shape of the hats were not analysed (25).

To date, no previous study has calculated the proportion of AC patients who specifically used lip photoprotection; therefore, our study

is the first AC prevalence study that described and analysed that specific type of photoprotection in AC patients.

Notably, we described the different clinical manifestations of AC (Fig. 8) and their possible associations with AC risk factors; these correlations have not been previously reported. Only a few studies have described the clinical characteristics of AC (Table 2).

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Table 2: The use of photoprotection and analysis of the clinical manifestations of AC in previous in AC prevalence studies.

Author	Photoprotection	AC clinical manifestations
Jorge Junior J *et al.* (13)	NA	NA
Campisi G *et al.* (14)	NA	NA
Espinoza I *et al.* (15)	NA	NA
Silva FD *et al.* (16)	No correlation between AC and general photoprotection. Use of sunscreen correlated with lower AC prevalence	The authors classify AC in mild, moderate and severe
Burke WA *et al.* (17)	NA	NA
Zanetti R *et al.* (18)	NA	NA
Henrique PR *et al.* (19)	NA	NA
Miranda AMO *et al.* (20)	NA	The authors classify AC in mild, moderate and severe
Martins-Filho PR *et al.* (21)	Cloth on the face combined with sunscreen correlated with lower AC incidence	The authors make reference to the distribution of clinical findings in an AC population
Junqueira JL *et al.* (22)	NA	NA
De Souza Lucena EE *et al.* (23)	Use of sunscreen and caps/hats correlated with AC prevalence	NA
De Oliveira Ribeiro A *et al.* (24)	Non-use of sunscreens correlated with AC prevalence	The authors make reference to the distribution of clinical findings in an AC population
Gheno JN *et al.* (25)	Use of hats showed a negative correlation with AC	NA
Silva MF *et al.* (26)	NA	NA
Ferreira AM *et al.* (27)	NA	NA

NA: Not analysed

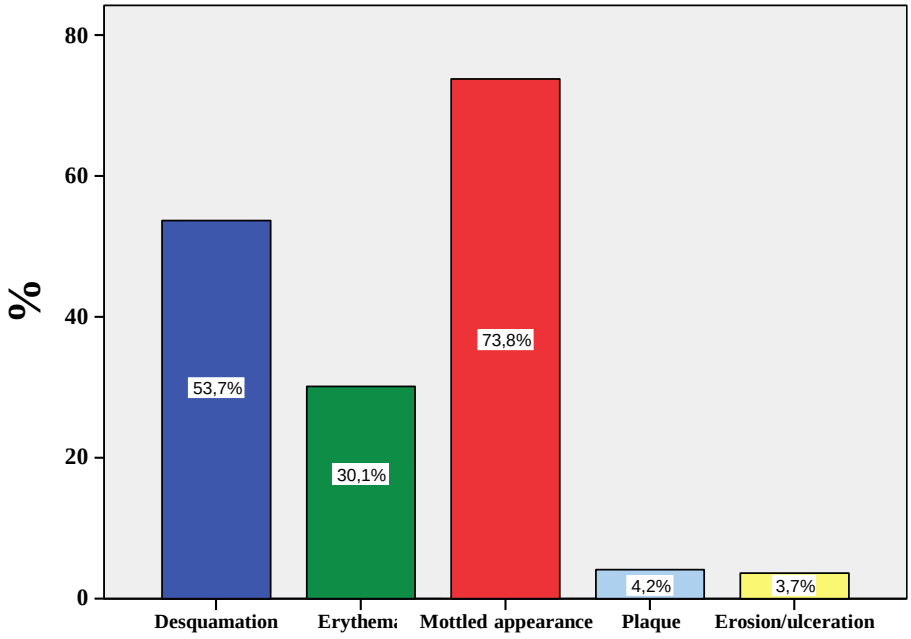

Figure 8: Clinical manifestations of AC.

Desquamation and erythema were associated with high alcohol intake and working outdoors for more than 25 years. The male sex was protective against desquamation, and present or past tobacco consumption was protective against erythema.

We found a significant association between a mottled appearance and a history of NMSC. Even though future studies are needed to confirm this correlation, the idea that a simple clinical sign may be able to predict a possible increased risk of NMSC carries much potential to be applied clinically.

Only 3.4% of our AC patients sought dermatologic advice for lip concerns indicating that very few were aware of the abnormal

presentation of their lip. This fact is especially relevant because 20.2% of our patients had been diagnosed with NMSC previously and, therefore, these patients should have been educated on self-examination of the mucosa and skin and correct photoprotection habits. These data indicate that clinicians and health authorities should promote primary and secondary prevention activities regarding actinic damage and skin cancer not only for the skin but also for the lips.

We detected typical indicators of actinic damage, AK and/or lentigines, in 73.5% of AC patients (32.1% presented with only lentigines, 21.8% presented with only AK and 19.6% presented with both lesions) (Fig. 9).

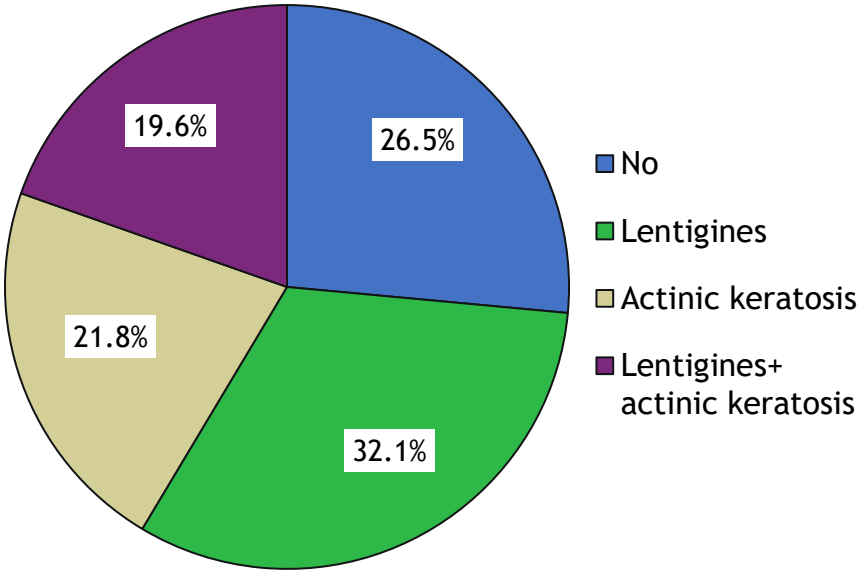

Figure 9: Presence of actinic damage indicators in AC patients.

AC patients aged > 65 years with Fitzpatrick skin phototypes I and II showed a statistically significant association with lentigines. The variables associated with the presence of AK in AC patients were Fitzpatrick skin phototypes I and II, age of > 65 years and a history of NMSC.

Patient age of > 65 years and Fitzpatrick skin types I and II and were associated with AK and lentigines in patients with AC. This is a consistent association because UV radiation is the main risk factor for the development of both these lesions (51-53). However, a history of NMSC was related only to AK and not lentigines, confirming the known correlation between NMSC (especially SCC) and AK, which is also considered *in situ* SCC.

To our knowledge, the risk factors associated with AK and lentigines in AC patients have not been reported previously. Furthermore, the high proportion of AC patients presenting with typical indicators of actinic damage (73.5%) should be a point of concern for clinicians. We recommend that clinical examination of the lips should be performed on all patients with actinic damage and the other way round, sun exposed skin should be explored in all patients with AC.

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9

STRENGTHS

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9. STRENGTHS

The main strengths of our study are mentioned in the discussion. They are summarised as follows:

- This is the first cross-sectional multi-centre AC prevalence study.

- Previous AC prevalence studies were mainly performed in specific populations (especially in South America); our study is the first multi-centre AC prevalence study in Europe, thus, a close correlation of AC prevalence in the Caucasian European populations aged 45 years or older is expected.

- We used a previously published, precise definition of AC to diagnose the patients in our study (24).

- Our sample size is sufficiently large to allow for solid conclusions.

- This is the first AC prevalence study to collect data on the Fitzpatrick skin phototypes and eye and hair colour of the subjects.

- This is the first AC prevalence study to collect data regarding the patients' history of malignant melanoma and NMSC.

- This the first AC prevalence study to show a significant correlation between a history of NMSC and the prevalence of AC.

- This is the first AC prevalence study to show that the risk of AC increases with age.

- This is the first European study to analyse specific lip photoprotection habits in a population with AC.

- This is the first study to describe different clinical manifestations of AC and their associated risk factors.

- This is the first study to describe the risk factors associated with the development of AK and lentigines in patients with AC.

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10
LIMITATIONS

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10. LIMITATIONS

There are several limitations to our study:

- We did not analyse the evolution of the patients as per the cross-sectional design of the study.

- Our patients were recruited from outpatient dermatology clinics and this may have added some bias because the general higher presence of females in dermatology clinics could have led to a high proportion of female patients with AC (54).

- Only patients on their "first visit" were allowed to participate; this excluded those who were being followed-up for other reasons, including AC, NMSC, etc.

- Only patients aged ≥ 45 years were selected for the study, which excluded younger patients with AC. Regardless, it is generally agreed that most cases of AC occur in people who are over 50 years of age (2,21,24,32).

- We could have quantified tobacco consumption more accurately by analysing pack-years rather than years of active smoking.

- Using a semiquantitative scale to calculate the frequency of lip photoprotection may have reduced the preciseness of our estimation. However, we attempted to correct this by calculating the number of sticks of protective lip balms used by the subjects in the previous year.

- We did not confirm AC histopathologically in most patients; the diagnoses were based on clinical features in more than 98% of patients. We biopsied 7 patients with uncertain lesions and our initial clinical suspicion of AC was confirmed in all of them.

- Inter-observer bias cannot be completely ruled out among the investigators, even though a precise definition of AC was established before starting the study and all the investigators were experienced dermatologists.

11
CONCLUSIONS

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11. CONCLUSIONS

1. AC is a prevalent condition in the Galician population among individuals aged 45 years and older.

2. Patients affected by AC in this population had an average age over 70 years and women were prevailing.

3. Subjects who were aged 60 years and older, had Fitzpatrick skin phototype II, had worked outdoors for >25 years and had a history of NMSC were at a higher risk of developing AC.

4. In subjects aged 60 years and older the risk of developing AC increased greatly with age.

5. The majority of AC patients did not practice lip photoprotection and even when they did, it was insufficient.

6. Only AC patients with Fitzpatrick's skin types I and II tended to use lip sun protection.

7. Promoting educational and preventive measures to address the importance of lip protection among the public will be beneficial, especially in high-risk populations.

8. Mottled appearance was the only clinical manifestation of AC that was significantly associated with a history of NMSC.

9. Other signs of actinic damage, such as AK and/or lentigines, were prevalent among AC patients.

10. AC patients aged 65 years and older and with Fitzpatrick skin phototypes I and II were at a higher risk of developing lentigines.

11. AC patients aged 65 years and older with Fitzpatrick skin phototypes I and II and a history of NMSC were at a higher risk of suffering from AK.

12. Very few subjects with AC sought dermatological advice regarding their lips, indicating a lack of concern regarding AC in the population.

13. Careful lip examination should be made mandatory for all patients with chronic actinic damage.

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APPENDIX: Accepted publications

Rodríguez-Blanco I, Flórez Á, Paredes-Suárez C, Rodríguez-Lojo R, González-Vilas D, Ramírez-Santos A, Paradela S, Suárez Conde I and Pereiro-Ferreirós M. ***Actinic cheilitis prevalence and risk factors: A cross-sectional multicentre study in a population aged 45 years and over in northwest Spain***. Acta Dermato-Venereologica 2018;98(10): 970-4 (47).

Last impact factor available (2019): 4.016

Impact factor in the year of publication (2018): 3.531.

Rank position 13/66, Q1.

https://www.medicaljournals.se/acta/content_files/files/pdf/98/10/5284.pdf

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Rodríguez-Blanco I, Flórez Á, Paredes-Suárez C, Rodríguez-Lojo R, González-Vilas D, Ramírez-Santos A, Paradela S, Suárez Conde I and Pereiro-Ferreirós M. ***Use of lip photoprotection in patients suffering from actinic cheilitis***. European Journal of Dermatology 2019;29(4):383-6 (48).

Impact factor in the year of publication (2019): 2.782

Rank position 23/68, Q2.

https://www.jle.com/download/ejd-315125-43584-use_of_lip_photoprotection_in_patients_suffering_from_actinic_cheilitis-a.pdf

Rodríguez-Blanco I, Flórez Á, Paredes-Suárez C, Rodríguez-Lojo R, González-Vilas D, Ramírez-Santos A, Paradela S, Suárez Conde I and Pereiro-Ferreirós M. ***Actinic cheilitis: Analysis of clinical subtypes, risk factors, and associated signs of actinic damage***. Acta Dermato-Venereologica 2019;99(10):931-2 (49).

Impact factor in the year of publication (2019): 4.016.

Rank position 7/68, Q1.

https://www.medicaljournals.se/acta/content_files/files/pdf/99/10/5503.pdf

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